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PATENT APPLICATION  
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**UNITED STATES PATENT APPLICATION**

of

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and

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for

**PROCESS FOR MANUFACTURING  
A PHARMACEUTICAL CHEWING GUM**

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**Docket No. 13352.6.1**

## FIELD OF THE INVENTION

The present invention relates to processes for producing chewing gum tablets as dosage forms for pharmaceutical therapeutic agents, and in particular to a process for making a pharmaceutical chewing gum dosage form having a more accurate and uniform dose of the pharmaceutical active ingredient.

## BACKGROUND

Pharmaceutical therapeutic agents, such as drugs, are formulated in a variety of dosage forms, depending upon the target absorption site of the drug, the intended time profile for absorption, the solubility characteristics of the drug, the susceptibility of the drug to various forms of attack in vivo, such as enzymatic degradation and organ uptake, and other considerations well-known to those skilled in the art. A large number of drugs are formulated in orally ingestible dosage forms for delivery into the gastrointestinal tract, where they are absorbed into the blood stream and carried to various organs or tissues where the pharmacological action is exerted. Typically, such dosage forms are capsules or tablets, which may further be provided with various coatings, to assist in passage through the gastrointestinal tract, or to provide a delayed or extended release profile. When more rapid therapeutic action is desired, or when the therapeutic agent is particularly susceptible to chemical or enzymatic attack in the gastrointestinal tract, a preferred route of delivery is injection into the blood stream, and the corresponding dosage form is an injectable liquid or solution. Still other drugs are delivered topically to the skin, eyes, and various mucosal tissues, in dosage forms such as ointments, creams, gels and lotions.

1 A number of therapeutically useful drugs are capable of buccal absorption; *i.e.*,  
2 absorption in the oral cavity, either sublingually or throughout the oral mucosal wall, or  
3 by dissolution in the saliva and absorption in the throat, esophagus, or upper  
4 gastrointestinal tract. For drugs having significant buccal and/or upper and lower  
5 gastrointestinal tract absorption, oral dosage forms taking advantage of the absorption,  
6 such as lozenges, chewable tablets, and chewing gum, are particularly advantageous.  
7 Such dosage forms permit more rapid therapeutic action compared to per-oral  
8 (swallowed) dosage forms, and the topically absorbed therapeutic agent also partially  
9 escapes liver metabolism.

10 The chewing gum dosage form is particularly attractive due to its ease of  
11 administration and the generally acceptable or even pleasant qualities of chewing gum.  
12 These attractive properties can significantly improve patient compliance with the dosage  
13 regimen. Thus, for example, U.S. Patent No. 4,971,079 is directed to chewing gum  
14 compositions having an anti-nicotine therapeutic effect, for use in facilitating cessation of  
15 smoking. Likewise, U.S. Patent No. 5,922,347 is directed to chewing gum compositions  
16 containing acetylsalicylic acid, a well-known anti-inflammatory and analgesic compound.

17 The conventional chewing gum processing technology involves melting a gum  
18 base in, for example, a sigma blender, and adding components such as sweeteners and  
19 flavorants to the melt. The melted mass is then extruded, rolled into sheets, and cut to the  
20 desired shape on the rollers. This conventional technology, however, suffers from  
21 several disadvantages, when applied to the preparation of pharmaceutical chewing gum  
22 dosage forms. For example, the elevated temperatures used in the melt can adversely  
23 affect the chemical stability of the therapeutic agent contained therein. In addition, the  
24 melting and mixing process of the highly viscous gum mass makes controlling the

1 accuracy and uniformity of the drug dose difficult, and this difficulty is further  
2 exacerbated by the lack of a precise form, shape or weight of the dosage form. Further,  
3 the gum processing technology is not easily adapted to incorporate the stringent sanitary  
4 manufacturing conditions required for production of pharmaceutical products, and the  
5 concomitant process validation and control measures. In addition, conventional gum  
6 processing technology is generally poorly suited for high-speed, more economical,  
7 production.

8 Several patents are directed to improved methods of processing chewing gums, in  
9 order to overcome some of the disadvantages described above. U.S. Patent No.  
10 4,000,321, for example, is directed to a process for preparing chewing gum, in which a  
11 chewing gum composition is cooled to -15 °C to facilitate fragmentation, and the cooled  
12 composition is pulverized with a crusher, hammer mill, pelletizer or turbomill. The  
13 pulverized product is then melted to cause the pulverized pieces to co-adhere, forming a  
14 chewing gum reportedly having low specific gravity and a soft chewing texture. The  
15 process, however, suffers from all of the disadvantages associated with heating, process  
16 speed, poorly defined dosage forms and weights described above, and is not well-suited  
17 for making a pharmaceutical chewing gum dosage form.

18 U.S. Patent No. 4,753,805 is directed to a chewing gum composition in the form  
19 of a tablet having a low moisture content. The tablet is produced by grinding a chewing  
20 gum composition, blending the ground composition with a compression aid, and  
21 compressing the granulated product to form a tablet. Grinding of the chewing gum  
22 composition, typically a difficult process because of the tendency for the gum to stick to  
23 the grinding apparatus, is accomplished by the use of 2-8% by weight of a grinding aid  
24 such as an alkaline metal phosphate, an alkaline earth metal phosphate, or a maltodextrin.

1 The use of such grinding aids, however, is disadvantageous. The metal phosphate salts  
2 are highly alkaline, and such alkalinity may be incompatible with acidic ionizable  
3 therapeutic agents, for example. In addition, the grinding aid remains in the composition  
4 and ultimately in the chewing gum tablet, and the presence of a large amount of metal  
5 phosphate in the dosage form is potentially problematic from therapeutic and safety  
6 perspectives.

7 Thus, there is a need for processes to produce dosage forms of buccally  
8 absorbable therapeutic agents which do not suffer from the disadvantages of conventional  
9 pharmaceutical chewing gum formulations.

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## SUMMARY OF THE INVENTION

It is an object of the present invention to provide a process for preparing chewing gum dosage forms of therapeutic agents topically effective toward the gastrointestinal tract having improved dose accuracy and uniformity.

It is also an object of the present invention to provide a process for preparing chewing gum dosage forms of therapeutic agents topically effective toward the gastrointestinal tract having a precise and well-defined form, shape and weight.

It is also an object of the present invention to provide a process for preparing chewing gum dosage forms of therapeutic agents topically effective toward the gastrointestinal tract, wherein the therapeutic agent is not subjected to elevated temperatures.

It is further an object of the present invention to provide processes for preparing chewing gum dosage forms of therapeutic agents topically effective toward the gastrointestinal tract capable of being carried out in high-speed, efficient manufacturing processes.

It is still a further object of the present invention to provide chewing gum dosage forms of therapeutic agents topically effective toward the gastrointestinal tract.

The foregoing objects and other advantages are achieved by the process of the present invention, in which a chewing gum composition is cooled to a temperature at which the composition is brittle, and the composition is ground while brittle to form a fine powder. In a preferred process, the composition is cooled by mixing with a coolant, such as solid carbon dioxide, and the mixture is ground to a powder. The powder can be mixed with a pharmaceutical active ingredient capable of buccal and/or upper or lower gastrointestinal tract topical absorption (*i.e.*, topically effective toward the gastrointestinal

1 tract), and formed into a tablet. Preferably, the mixture of the powder, pharmaceutical  
2 active ingredient, and other additives such as coating agents, binders, additional active  
3 ingredients, and sweeteners, are granulated in a fluidized bed granulator prior to forming  
4 the mixture into a tablet. The resulting tablet provides an improved dosage form of the  
5 pharmaceutical active ingredient.

6 Thus, in one aspect, the present invention provides a process for preparing a  
7 chewing gum tablet, the process including the steps of cooling a chewing gum  
8 composition to a temperature at which the composition is brittle, grinding the cooled  
9 chewing gum composition, and forming the ground chewing gum composition into a  
10 tablet.

11 In another aspect, the present invention provides a process for preparing a  
12 chewing gum tablet, the process including the steps of providing a mixture including a  
13 chewing gum composition and solid carbon dioxide, grinding the mixture to form a  
14 powder, removing the solid carbon dioxide from the powder, and forming the powder  
15 into a tablet.

16 In another aspect, the present invention provides a process for preparing a dosage  
17 form of an active ingredient topically effective toward the gastrointestinal tract, the  
18 process including the steps of providing a mixture including a chewing gum composition  
19 and solid carbon dioxide, grinding the mixture to form a powder, removing the solid  
20 carbon dioxide from the powder, mixing the powder with a composition including the  
21 active ingredient to form an active ingredient-containing powder, granulating the active  
22 ingredient-containing powder in a fluidized bed granulator, and compressing the granules  
23 into a tablet to form a dosage form containing the active ingredient.

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In another aspect, the present invention provides a chewing gum dosage form of an active ingredient topically effective toward the gastrointestinal tract, the dosage form including a gum base and an active ingredient and being formed of a plurality of compressed granules containing the gum base and active ingredient.

These and other objects and features of the present invention will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.



**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

The present invention is directed to processes for improved production of pharmaceutical chewing gum dosage forms. The processes of the present invention enable production of chewing gum tablets without the disadvantages of heating the therapeutic agent, and without problems associated with inaccuracy and non-uniformity of therapeutic agent doses characteristic of conventional chewing gum processes. The present invention achieves these and other significant advantages by a process in which a chewing gum composition is cooled to a brittle temperature, ground while at a brittle temperature to form a powder, and formed into a tablet. The pharmaceutical therapeutic agent, or active ingredient, is readily mixed with the powdered gum composition prior to tablet formation, to produce a uniform and accurate mixture, from which a well-defined and precise tablet dosage form can be prepared by tabletization.

In one step of the process of the present invention, a chewing gum composition is cooled to a temperature at which the composition is brittle. The chewing gum composition can be any chewing gum composition, such as conventional compositions known in the art. In general, such compositions include a chewing gum base, to which may be added flavorants, sweeteners, colorants, and other ingredients known in the art. The chewing gum base is typically a natural or synthetic elastomer, such as rubber, chicle, lechi caspi, jelutong, polyisobutylene, an isobutylene-isoprene copolymer, a styrene-butadiene copolymer, or other suitable gum base known in the art. In order to facilitate the subsequent grinding step, the chewing gum composition is preferably in the form of chips, pellets, or other relatively small particles.

The chewing gum composition is cooled to a temperature at which the composition is brittle. It should be appreciated that even a mildly cooled chewing gum

1 composition will possess some degree of brittleness; however, to be suitable for the  
2 process of the present invention, the composition is cooled to a temperature at which the  
3 composition is sufficiently brittle such that the brittleness is maintained during the  
4 subsequent grinding step without adhesion to the grinding apparatus. The appropriate  
5 temperature is determined in part by the specific composition of the chewing gum, and is  
6 easily determined empirically by observing the properties of the cooled chewing gum  
7 composition. Thus, for example, a chewing gum composition cooled to a temperature  
8 sufficiently low can be ground in, for example, a mill grinder, without the composition  
9 sticking to the grinder parts. Preferably, the temperature will be less than  $-15^{\circ}\text{C}$ , more  
10 preferably less than  $-30^{\circ}\text{C}$ , and still more preferably less than about  $-40^{\circ}\text{C}$ .

11 The cooling can be carried out by any of a variety of cooling processes. The  
12 chewing gum composition can be frozen in a conventional freezer apparatus capable of  
13 reaching the very low temperatures needed to achieve the requisite brittleness.  
14 Preferably, however, the chewing gum composition is cooled by contacting with a  
15 coolant. The coolant can be any substance capable of cooling the chewing gum  
16 composition to the desired temperature and can be, for example, a cryogenic liquid such  
17 as liquid nitrogen, a cold solid such as solid carbon dioxide, or a cold gas such as the  
18 gaseous boil-off from a cryogenic liquid. The coolant should be chosen so that the  
19 coolant does not interact adversely with the chewing gum composition or with the mixing  
20 or grinding apparatuses used in the present process. In addition, the coolant should not  
21 produce a substance upon warming that suffers from such adverse interactions, or that  
22 leaves a residue that adversely affects subsequent processing or presents potential safety  
23 hazards when the chewing gum tablet is chewed. For example, a coolant such as water  
24 ice, even if cooled to a sufficiently low temperature, would not be preferred, as any water

1 ice that melts will form liquid water, which is absorbed by the chewing gum composition.  
2 Likewise, a coolant such as a hydrocarbon slush would not be preferred, since any  
3 hydrocarbon residue remaining in the chewing gum composition would present potential  
4 safety hazards when the chewing gum tablet is consumed.

5 In accordance with the present invention, and in a particularly preferred aspect, it  
6 has been surprisingly found that by mixing a chewing gum composition with solid carbon  
7 dioxide (dry ice), the chewing gum composition can be cooled to a brittle temperature  
8 without the undesirable effects discussed above. At the sublimation temperature, -78.5  
9 °C, solid carbon dioxide is sufficiently cold to ensure that the chewing gum composition  
10 is suitably brittle. Of course, the solid carbon dioxide can be cooled to an even lower  
11 temperature, if desired. Upon warming, the solid carbon dioxide sublimates to form carbon  
12 dioxide gas, which does not react with the chewing gum composition, is not absorbed by  
13 the composition, and does not interact adversely with processing apparatuses. Further,  
14 the gaseous, non-reactive nature of the sublimation product ensures that no undesirable  
15 and potentially hazardous residue of the coolant remains in the chewing gum tablet  
16 product. Preferably, the solid carbon dioxide coolant is provided in pelletized form to  
17 facilitate further processing steps.

18 Alternatively, the steps of cooling the chewing gum composition and grinding the  
19 composition can be combined into a single step by, for example, cooling the grinding  
20 apparatus itself, such as by contacting the grinding apparatus with a coolant. For  
21 example, in this alternative aspect, the grinding apparatus can be placed in a cooling  
22 jacket of liquid nitrogen or other cold liquid. For more efficient cooling, in this  
23 embodiment, the chewing gum composition is preferably pre-cooled, although the pre-  
24 cooling need not be to a temperature as low as the brittle temperature. It should be

1 appreciated that even in the preferred embodiment, wherein the chewing gum  
2 composition is cooled by mixing with a coolant, it may also be advantageous to cool the  
3 grinding apparatus as well.

4 If desired, the chewing gum composition can be mixed with an anti-caking agent  
5 prior to the grinding step, and the use of an anti-caking agent is preferred. Such anti-  
6 caking agents are known in the art. A preferred anti-caking agent is precipitated silicon  
7 dioxide. In a preferred embodiment in which the chewing gum composition is mixed  
8 with solid carbon dioxide and an anti-caking agent prior to grinding, the anti-caking agent  
9 helps to prevent agglomeration of the subsequently ground chewing gum particles, upon  
10 sublimation of the solid carbon dioxide.

11 If a coolant, such as solid carbon dioxide, and other components, such as an anti-  
12 caking agent are used, the chewing gum composition and other substances can be  
13 combined using a conventional mixing apparatus, such as a vented V-blender.

14 The chewing gum composition, and other components such as coolant and anti-  
15 caking agent, are ground to form a fine powder. The grinding can be carried out using  
16 any conventional grinding apparatus, such as a mill grinder. In a preferred embodiment,  
17 a mixture of a chewing gum composition, solid carbon dioxide, and precipitated silica is  
18 provided, and the mixture is introduced into a mill grinder. In this embodiment, the  
19 mixture is ground to a fine powder, and the solid carbon dioxide remains present during  
20 the grinding process. It has been surprisingly found that by co-grinding the chewing gum  
21 composition and solid carbon dioxide, the chewing gum composition can be ground into  
22 a fine powder, without any adverse adhesion to the grinding apparatus.

23 The desired properties of the ground chewing gum composition are better  
24 achieved when the composition is kept at a very low temperature throughout the grinding

1 process. Thus, in a particularly preferred process, a mixture of chewing gum  
2 composition, solid carbon dioxide and precipitated silica is ground in a mill grinder in a  
3 first grinding step, additional solid carbon dioxide and precipitated silica are added to the  
4 ground composition, and the composition is further ground in a second grinding step.  
5 This two-step grinding process advantageously keeps the chewing gum composition at a  
6 very low temperature. Although not wishing to be bound by theory, it is further believed  
7 that the presence of the solid carbon dioxide particles, in addition to providing the  
8 necessary cooling, also serves to enhance the efficiency of the grinding process. It should  
9 be appreciated that although a two-step grinding process is described herein, the number  
10 of steps is not particularly limited. Thus, a process in which additional solid carbon  
11 dioxide and/or precipitated silica are added in multiple steps, or even in a slow,  
12 continuous stream, may also be used if desired.

13 After the composition is ground to a powder, the coolant can be removed by, for  
14 example, allowing the coolant to evaporate. Using the preferred coolant of solid carbon  
15 dioxide, the coolant is removed simply by allowing the solid carbon dioxide to sublime,  
16 releasing harmless carbon dioxide gas and leaving no undesirable contaminants. The  
17 ground composition can be stored such that the carbon dioxide gas can escape, as for  
18 example in loosely closed plastic bags. Alternatively, the carbon dioxide can be removed  
19 more rapidly by processing the ground composition in a fluidized bed reactor.

20 Once the coolant has been removed from the powder, the powder can be mixed  
21 with other ingredients as desired, before forming the powder into a tablet. Such  
22 ingredients can be any ingredient known to be incorporated into chewing gum and not  
23 incompatible with tablet formation, such as coating agents, binders, lubricants,  
24 sweeteners and the like. Preferably, a pharmaceutical active ingredient topically effective

1 toward the gastrointestinal tract is added in an amount such that the tablet ultimately  
2 formed includes a therapeutically effective dose of the active ingredient. As used herein,  
3 the term "topically effective toward the gastrointestinal tract" means having significant  
4 absorption in the buccal cavity and/or the mucous layer of the upper and/or lower  
5 gastrointestinal tract. The active ingredient can be any active ingredient having such  
6 topical absorption, such as, for example, gastrointestinal anti-infective drugs, anti-  
7 diarrheal drugs, anti-cholic drugs, cardiovascular drugs such as nitroglycerin, and  
8 calcium channel blocking agents such as nifedipine.

9 Such ingredients can be combined with the powder by blending, in for example, a  
10 sigma mill, or a high shear mixer. If a conventional blending apparatus is used, the  
11 powder mixture should include sufficient amounts of binder to enable effective  
12 processing of the mixture. Such binders, well-known in the art, are typically aqueous,  
13 and the large amounts of aqueous binder necessary to enable tabletization from a blended  
14 mixture are not preferred, as the mixture tends to swell and to develop a disadvantageous  
15 stickiness that makes tabletization less efficient. However, although not preferred, such  
16 blending processes can still be used in the process of the present invention.

17 In a preferred process, it has been surprisingly found that the powdered chewing  
18 gum composition produced by the process described above can be combined with other  
19 ingredients, such as coating agents, binders, sweeteners and active ingredients, in a  
20 fluidized bed reactor. The use of a fluidized bed reactor is particularly advantageous, as  
21 the process partially rebuilds the powder into granules, as well as coats the powder  
22 particles and/or granules with a coating agent, thereby minimizing undesired particle  
23 agglomeration. In this embodiment, the temperature of the process should be controlled.  
24 If the temperature is too low, the mixture (the "blend") will stick because of a low

1 evaporation rate as the binding solution is sprayed on the blend. The granules that  
2 develop are then too large for subsequent tabletization. If the temperature is too high, the  
3 blend can soften, with the same disadvantageous results. With these considerations in  
4 mind, one skilled in the art can readily determine the appropriate process temperature by  
5 observing and optimizing the properties of the granules produced. To reduce the  
6 processing time, the fluid bed granulator can be pre-heated to the chosen processing  
7 temperature prior to adding the powder mixture. After granulation, the granulate can be  
8 discharged onto screens, and any granules that are too large can be removed.

9 In a preferred process, the powder mixture, containing the powdered chewing  
10 gum composition, active ingredient, and other additives, is weighed into individual  
11 "charges" for the fluid bed granulator. After processing as described above, and  
12 screening, the individual charges are then preferably recombined and mixed in a V-  
13 blender, and the resultant "cross-blend" is then discharged across a screen to again  
14 remove any granules that are too large. It is particularly advantageous to sample the  
15 cross-blend discharge by taking multiple samples from the discharge stream, for analysis  
16 of the active ingredient. Thus, the discharge mixture can be stored while the multiple  
17 samples are analyzed, to insure that the desired level and uniformity of level of active  
18 ingredient are present. If necessary, additional active ingredient can then be added.

19 The discharge mixture is again placed in a V-blender, and any additional active  
20 ingredient added. In addition, an anti-adherent is preferably added at this time, along  
21 with any other desired excipients or inactive ingredients. A preferred anti-adherent is  
22 talc. The mixture can then be discharged, again screened, and staged for compression.

23 Compression to form tablets can be carried out by any conventional process, such  
24 as a punching process. Of course, the punching process should be monitored for signs of

1 sticking to the punches, and the apparatus cleaned, and/or coated with additional anti-  
2 adherent as needed.

3 In another aspect, the present invention is directed to chewing gum dosage forms  
4 of a pharmaceutical active ingredient topically effective toward the gastrointestinal tract,  
5 the dosage form being a tablet formed of compressed granules of a gum base and the  
6 active ingredient. The granules forming the tablet can be of a size convenient for  
7 tabletization, typically from about 15 to about 30 mesh size, and preferably about 20 to  
8 about 25 mesh size. The tablets can be produced by any of the methods described above.  
9 Advantageously, the tablet does not contain any residue of a grinding aid, such as an  
10 alkaline phosphate.

11 The present invention may be embodied in other specific forms without departing  
12 from its spirit or essential characteristics. The described embodiments are to be  
13 considered in all respects only as illustrative and not restrictive. The scope of the  
14 invention is, therefore, indicated by the appended claims rather than by the foregoing  
15 description. All changes which come within the meaning and range of equivalency of the  
16 claims are to be embraced within their scope.

17 What is claimed and desired to be secured by United States Letters Patent is:  
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